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(54) Title: INJECTABLE SUSTAINED RELEASE DELIVERY SYSTEM WITH LOPERAMIDE

(57) Abstract: The present invention provides for a flowable composition suitable for use as a controlled release implant, a method for forming a flowable composition for use as a controlled release implant, and methods for using the flowable composition. The composition comprises a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid; a biocompatible organic solvent that is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester; and an antihyperalgesic opiate.

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INJECTABLE SUSTAINED RELEASE DELIVERY SYSTEM WITH LOPERAMIDE

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Background of the Invention

Pain is the effect of noxious stimuli on nerve endings of a subject which results in the transmission of impulses to the cerebrum. This sensation informs the subject of actual or impending tissue damage and elicits a defensive response. The degree of response substantially correlates with the degree of noxious stimuli in order to quickly avoid further tissue damage and to reestablish normal pre-injury conditions in the subject. The sensation of pain, however, does not end with the stoppage of the noxious stimuli but continues to persist during the inflammation stage of the injury. In turn, the continuation of pain perception causes discomfort to, and deleteriously affects the well-being of, the subject. It is, therefore, important to reduce and/or eliminate pain perception of a subject subsequent to injuries.

The reduction/elimination of pain perception can be affected by the central nervous system (hereinafter sometimes referred to as CNS)-mediated analgesia which leads to an overall inhibition of the pain transmission. CNS-mediated analgesia can be effected by systemically administered opiates which, by interaction with specific receptors in the brain and spinal cord, are able to block pain transmission. Systemic opiates, such as morphine, which have been used for many years to control post injury pain, have side effects because their actions within the brain include sedation, depression of respiration, constipation, nausea and development of addiction and dependence. When peripherally applied, opiates have a short duration of action and still possess the undesirable side effects.

Certain opiates, such as loperamide [i.e., 4-(p-chlorophenyl)-4-hydroxy-N-N-dimethyl- α -diphenyl-1-piperidinebutyramide hydrochloride] and its analogs were reported to be devoid of CNS effects. This is believed to be due to the failure of the opiates to cross the blood brain barrier. Loperamide hydrochloride has been used for a long time in antidiarrheal formulations and

has been completely free of the undesirable CNS effects. It is preferable to use such opiates to inhibit/eliminate post-injury pain without concomitant CNS effects.

Spray formulations for topical application of loperamide hydrochloride to a site of injury are known. See, e.g., U.S. Patent No. 5,811,078; U.S. Patent No. 5,798,093; U.S. Patent No. 5,763,445; U.S. Patent No. 5,760,023; U.S. Patent No. 5,744,458; U.S. Patent No. 5,849,762; and references cited therein. Loperamide hydrochloride is sparingly soluble in water. To provide for the inhibition of pain, very large amounts of loperamide hydrochloride are required. The use of such large amounts result in clogging of the spray nozzle and deposition of the compounds on the wall of the container from which the aqueous solution of the compounds are dispensed.

While loperamide hydrochloride is soluble in organic solvents, the use of such solvents are very limited for treating topical injuries. The organic solvents having oily consistency tend to hold the active compound and do not allow quick and sufficient release to the site of injury to be treated. Other organic solvents without oily consistency, such as methanol, have deleterious affects on open wounds through which they can enter the blood circulation system.

Ethanol, propanol and isopropanol have been selected as carriers in which loperamide hydrochloride is soluble and which can be used on open wounds without deleterious side effects. However, these vehicles resulted in a substantial amount of stinging and/or burning sensations, rendering the vehicles unsuitable for the delivery of the active agent. Although, during the period of spraying a pleasant cooling effect was observed, the subsequent absorption of the vehicle increased the pain already present at the site of injury.

U.S. Patent No. 5,700,485 discloses biodegradable controlled release microspheres for the prolonged administration of a local anesthetic agent (e.g., dibucaine, lidocaine, tertacaine, etc.). See, e.g., Abstract and column 4, lines 22-30. Prolonged release of the anesthetic agent is obtained by the incorporation of a glucocorticoid (e.g., dexamethasone) into the polymeric matrix or by co-administration of the glucocorticoid with the microspheres. See,

e.g., Abstract. The '485 patent does not disclose or suggest, however, that the glucocorticoid can be employed to prevent or diminish erythema and/or edema to the surrounding tissue. In addition, the '485 patent does not disclose or suggest that an antihyperalgesic opiate (i.e., narcotic analgesic) such as loperamide, can be used *in lieu* of the local anesthetic agent, to be distributed throughout the local area of injury.

Accordingly, what is needed is a suitable carrier system containing an effective amount of loperamide hydrochloride that can deliver the drug to a site of injury. The suitable carrier should deliver the effective amount of loperamide hydrochloride such that the drug will be distributed throughout the local area of injury.

Summary of the Invention

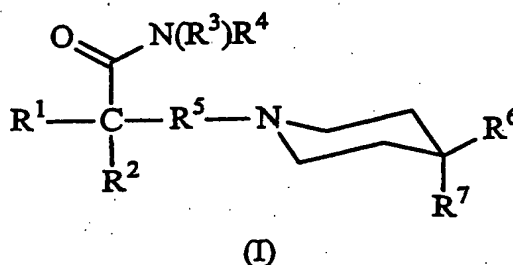
The present invention provides a flowable composition, a biodegradable implant formed in situ, and a solid implant that includes an antihyperalgesic opiate, such as loperamide, that can be effectively delivered to a site of injury. The need to dissolve the antihyperalgesic opiate, such as loperamide, in a carrier such as water has been obviated. In addition, relatively large amounts (e.g., 5 grams or more) of the antihyperalgesic opiate, such as loperamide, is not required in the present invention. Neither the flowable composition, the biodegradable implant formed in situ, nor the solid implant of the present invention include as the carrier organic solvents that have deleterious side effects or that increase the pain already present at the site of injury. The flowable composition, the biodegradable implant formed in situ, and the solid implant of the present invention can deliver an effective amount of loperamide to a site of injury. The flowable composition, the biodegradable implant formed in situ, and the solid implant of the present invention can effectively deliver the loperamide such that it will be distributed throughout the local area of injury. The flowable composition, the biodegradable implant formed in situ, and the solid implant of the present invention will cause little or no erythema, edema, or combination thereof, to surrounding tissue.

The present invention provides a flowable composition suitable for use as a controlled release implant. The composition includes a biodegradable thermoplastic polyester, a biocompatible organic solvent, and an antihyperalgesic opiate. The biodegradable thermoplastic polyester is at least substantially insoluble in aqueous medium or body fluid. In one embodiment of the present invention, the biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a polycaprolactone, a polyanhydride, a polyamide, a polyurethane, a polyesteramide, a polyorthoester, a polydioxanone, a polyacetal, a polyketal, a polycarbonate, a polyorthocarbonate, a polyphosphazene, a polyphosphoester, a polyhydroxybutyrate, a polyhydroxyvalerate, a polyalkylene oxalate, a polyalkylene succinate, a poly(malic acid) polymer, a polymaleic anhydride, a poly(methylvinyl) ether, a poly(amino acid), chitin, chitosan, a copolymer thereof, a terpolymer thereof, or any combination thereof. In another embodiment of the present invention, the biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof. In another embodiment of the present invention, the biodegradable thermoplastic polyester is poly (DL-lactide-co-glycolide). In one embodiment of the present invention, the biodegradable thermoplastic polyester is present in about 10 wt.% to about 80 wt.% of the composition. In one embodiment of the present invention, the biodegradable thermoplastic polyester has an average molecular weight of about 4,000 to about 45,000.

In one embodiment of the present invention, the biocompatible organic solvent is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester. In one embodiment of the present invention, the biocompatible organic solvent is N-methyl-2-pyrrolidone, 2-pyrrolidone, 2-ethoxyethanol, 2-ethoxyethyl acetate, ethyl acetate, ethyl lactate, ethyl butyrate, diethyl malonate, diethyl glutarate, tributyl citrate, acetyltri-n-hexylcitrate, diethyl succinate, tributyrin, isopropyl myristate, propylene carbonate, dimethyl carbonate, ethylene glycol dimethyl ether, propylene glycol, 1,3-butylene glycol, ϵ -caprolactone, γ -butyrolactone, N,N-dimethylformamide, dimethylacetamide, dimethyl sulfoxide, dimethyl sulfone, caprolactam, decylmethylsulfoxide, oleic acid, N,N-dimethyl-m-toluamide, 2,2 dimethyl-1,3-

dioxolane-4-methanol, triacetin, ethyl acetate, benzyl alcohol, benzyl benzoate, solketal, glycofurol, 1-dodecylazacycloheptan-2-one, or any combination thereof. In another embodiment of the present invention, the biocompatible polar aprotic solvent is N-methyl-2-pyrrolidone, 2-pyrrolidone, N, N-dimethylformamide, dimethyl sulfoxide, propylene carbonate, caprolactam, triacetin, ethyl acetate, or any combination thereof. In another embodiment of the present invention, the biocompatible polar aprotic solvent is N-methyl-2-pyrrolidone. In one embodiment of the present invention, the biocompatible organic solvent is a biocompatible polar aprotic solvent. In one embodiment of the present invention, the biocompatible organic solvent is present in about 20 wt.% to about 90 wt.% of the composition.

In one embodiment of the present invention, the antihyperalgesic opiate is a compound of formula (I):



wherein

R¹ is aryl, heteroaryl, aryl (C₁-C₆)alkyl, or heteroaryl (C₁-C₆)alkyl;

R² is aryl, heteroaryl, aryl (C₁-C₆)alkyl, or heteroaryl (C₁-C₆)alkyl;

R³ is (C₁-C₆)alkyl;

R⁴ is (C₁-C₆)alkyl;

R⁵ is (C₁-C₆)alkyl;

R⁶ is cyano, halo, hydroxy, NR⁸R⁹ or COOR¹⁰;

R⁷ is aryl, heteroaryl, aryl (C₁-C₆)alkyl, or heteroaryl (C₁-C₆)alkyl;

wherein any aryl, heteroaryl, or alkyl of R¹-R⁷ is optionally substituted on carbon with one or more (C₁-C₆)alkyl, (C₁-C₆)alkoxy, cyano, halo, nitro, trifluoromethyl, hydroxy, NR⁸R⁹, COOR¹⁰, SR¹¹, or CON(H)R¹²;

R⁸-R¹² are each independently hydrogen or (C₁-C₆)alkyl; or a pharmaceutically acceptable salt thereof.

In one embodiment of the present invention, R¹ is phenyl, R² is phenyl, R³ is methyl, R⁴ is methyl, R⁵ is ethyl, R⁶ is hydroxy, and R⁷ is para-chlorophenyl.

In one embodiment of the present invention, the antihyperalgesic opiate is a non central nervous system type opiate. In one embodiment of the present invention, the antihyperalgesic opiate is 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl- α,α -diphenyl-1-piperidinebutanamide; or a pharmaceutically acceptable salt thereof. In one embodiment of the present invention, the antihyperalgesic opiate is present in about 1.0 wt.% to about 20.0 wt.% of the composition. In one embodiment of the present invention, the composition has a volume of about 0.1 mL to about 5.0 mL. In one embodiment of the present invention, the composition is formulated for administration about once per three days to about once per thirty days.

In one embodiment of the present invention, the flowable composition, biodegradable implant formed in situ, solid implant, or combination thereof, can optionally include a glucocorticoid (e.g., betamethasone) to diminish the likelihood that there will be erythema, edema, or a combination thereof to surrounding tissue.

The present invention also provides for a method for forming a flowable composition for use as a controlled release implant. The method includes the step of mixing, in any order a biodegradable thermoplastic polyester as illustrated above, a biocompatible organic solvent as illustrated above, and an antihyperalgesic opiate as illustrated above. The mixing is performed for a

sufficient period of time effective to form the flowable composition for use as a controlled release implant. In one embodiment of the present invention, the biocompatible thermoplastic polyester and the biocompatible organic solvent are mixed together to form a mixture and the mixture is then mixed with the antihyperalgesic opiate to form the flowable composition.

The present invention also provides for a biodegradable implant formed in situ, in a patient. The biodegradable implant is formed from the steps of injecting a composition within the body of the patient and allowing the biocompatible organic solvent to dissipate to produce a solid biodegradable implant. The composition includes an effective amount of a biodegradable thermoplastic polyester as illustrated above, an effective amount of a biocompatible organic solvent as illustrated above, and an effective amount of an antihyperalgesic opiate as illustrated above. In one embodiment of the present invention, the patient is a mammal. In one embodiment of the present invention, the mammal is a human. In one embodiment of the present invention, the solid implant releases the effective amount of antihyperalgesic opiate as the solid implant biodegrades in the patient.

The present invention also provides for a method of forming a biodegradable implant in situ, in a living patient. The method includes the steps of injecting a flowable composition within the body of a patient and allowing the biocompatible organic solvent to dissipate to produce a solid biodegradable implant. The flowable composition includes an effective amount of a biodegradable thermoplastic polyester as illustrated above, an effective amount of a biocompatible organic solvent as illustrated above, and an effective amount of an antihyperalgesic opiate as illustrated above. In one embodiment of the present invention, the solid biodegradable implant releases the effective amount of antihyperalgesic opiate by diffusion, erosion, or a combination of diffusion and erosion as the solid implant biodegrades in the patient. In one embodiment of the present invention, the patient is a mammal. In one embodiment of the present invention, the mammal is a human.

The present invention also provides for a method of treating or preventing pain in a patient. The method includes administering to the patient in

need of such treatment or prevention an effective amount of a flowable composition of the present invention. In one embodiment of the present invention, the patient is a mammal. In one embodiment of the present invention, the mammal is a human.

5 The present invention also provides for a kit. The kit includes a first container that contains a composition that includes a biodegradable thermoplastic polyesters as illustrated above and a biocompatible organic solvent as illustrated above. The kit also includes a second container that contains an antihyperalgesic opiate as illustrated above. In one embodiment of the present
10 invention, the first container is a syringe. In one embodiment of the present invention, the second container is a syringe. In one embodiment of the present invention, the kit includes instructions. In one embodiment of the present invention, the first container can be connected to the second container. In
15 another embodiment of the present invention, the first container and the second container are each configured to be directly connected to each other.

 The present invention also provides for a solid implant. The solid implant includes a biocompatible thermoplastic polyester as illustrated above and an antihyperalgesic opiate as illustrated above. The solid implant has a solid or gelatinous microporous matrix, the matrix being a core surrounded by a skin.
20 In one embodiment of the present invention, the solid implant further includes a biocompatible organic solvent as illustrated above. In one embodiment of the present invention, the amount of biocompatible organic solvent is minimal. In one embodiment of the present invention, the amount of biocompatible organic solvent decreases over time. In one embodiment of the present invention, the
25 core contains pores of diameters from about 1 to about 1000 microns. In one embodiment of the present invention, the skin contains pores of smaller diameters than those of the core pores. In one embodiment of the present invention, the skin pores are of a size such that the skin is functionally non-porous in comparison with the core.

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Detailed Description of the Invention

The present invention provides a flowable composition, a biodegradable implant formed in situ, and a solid implant that includes an antihyperalgesic opiate, such as loperamide, that can be effectively delivered to a site of injury. The need to dissolve the antihyperalgesic opiate, such as loperamide, in a carrier such as water has been obviated. In addition, relatively large amounts (e.g., 5 grams or more) of the antihyperalgesic opiate, such as loperamide, is not required in the present invention. Neither the flowable composition, the biodegradable implant formed in situ, nor the solid implant of the present invention include as the carrier organic solvents that have deleterious side effects or that increase the pain already present at the site of injury. The flowable composition, the biodegradable implant formed in situ, and the solid implant of the present invention can deliver an effective amount of loperamide to a site of injury. The flowable composition, the biodegradable implant formed in situ, and the solid implant of the present invention can effectively deliver the loperamide such that it will be distributed throughout the local area of injury.

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl and alkoxy denote both straight and branched groups; but reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic. Heteroaryl encompasses a radical attached via a ring carbon of a monocyclic aromatic ring containing five or six ring atoms consisting of carbon and one to four heteroatoms each selected from the group consisting of non-peroxide oxygen, sulfur, and N(X) wherein X is absent or is H, O, (C₁-C₆)alkyl, phenyl or benzyl, as well as a radical of an ortho-fused bicyclic heterocycle of about eight to ten ring atoms derived therefrom, particularly a benz-derivative or one derived by fusing a propylene, trimethylene, or tetramethylene diradical thereto.

It will be appreciated by those skilled in the art that compounds disclosed herein having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to

be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound disclosed herein, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine antihyperalgesic activity using tests which are well known in the art.

Specific and preferred values listed below for radicals, substituents, biodegradable thermoplastic polyesters and biocompatible organic solvents; ranges of thermoplastic polyesters, biocompatible organic solvents, antihyperalgesic opiate, and flowable compositions; molecular weights of the thermoplastic polyester; ranges of the solid implant described herein below are for illustration only; they do not exclude other radicals, substituents, biodegradable thermoplastic polyesters and biocompatible organic solvents; ranges of thermoplastic polyesters, biocompatible organic solvents, antihyperalgesic opiate, and flowable compositions; molecular weights of the thermoplastic polyester; and ranges of the solid implant.

Specifically, (C₁-C₆)alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; (C₁-C₆)alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 3-pentoxy, or hexyloxy; aryl can be phenyl, indenyl, or naphthyl; and heteroaryl can be furyl, imidazolyl, triazolyl, triazinyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, pyrazinyl, tetrazolyl, pyridyl, (or its N-oxide), thienyl, pyrimidinyl (or its N-oxide), indolyl, isoquinolyl (or its N-oxide) or quinolyl (or its N-oxide).

The present invention provides a flowable composition suitable for use as a controlled release implant, a method for forming the flowable composition, a method for using the flowable composition, the biodegradable implant that is formed in situ from the flowable composition, a method of forming the biodegradable implant in situ, a method for using the biodegradable implant that is formed in situ, a kit that includes the flowable composition, and

the solid implant. The flowable composition may be used to provide a biodegradable or bioerodible microporous in situ formed implant in animals. The flowable composition is composed of a biodegradable thermoplastic polymer or copolymer in combination with a suitable biocompatible organic solvent. The biodegradable thermoplastic polyesters or copolymers are substantially insoluble in water and body fluid, biocompatible, and biodegradable and/or bioerodible within the body of an animal. The biocompatible organic solvent is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester. The flowable composition is administered as a liquid or gel to tissue wherein the implant is formed in situ. The composition is biocompatible and the polymer matrix does not cause substantial tissue irritation or necrosis at the implant site. The implant can be used to deliver an antihyperalgesic compound.

Preferably, the flowable composition can be a liquid or a gel, suitable for injection in a patient (e.g., human). As used herein, "flowable" refers to the ability of the composition to be injected through a medium (e.g., syringe) into the body of a patient. For example, the composition can be injected, with the use of a syringe, beneath the skin of a patient. The ability of the composition to be injected into a patient will typically depend upon the viscosity of the composition. The composition will therefore have a suitable viscosity, such that the composition can be forced through the medium (e.g., syringe) into the body of a patient. As used herein, a "liquid" is a substance that undergoes continuous deformation under a shearing stress. Concise Chemical and Technical Dictionary, 4th Enlarged Ed., Chemical Publishing Co., Inc., p. 707, NY, NY (1986). As used herein, a "gel" is a substance having a gelatinous, jelly-like, or colloidal properties. Concise Chemical and Technical Dictionary, 4th Enlarged Ed., Chemical Publishing Co., Inc., p. 567, NY, NY (1986).

Biodegradable Thermoplastic Polyester

A thermoplastic composition is provided in which a solid, biodegradable polyester and an antihyperalgesic opiate are dissolved in a

biocompatible organic solvent to form a flowable composition, which can then be administered, e.g., via a syringe and needle. Any suitable biodegradable thermoplastic polyester can be employed, provided the biodegradable thermoplastic polyester is at least substantially insoluble in aqueous medium or body fluid. Suitable biodegradable thermoplastic polyesters are disclosed, e.g., in U.S. Patent Nos. 4,938,763; 5,707,647; 5,702,716; 5,632,727; 5,599,552; 5,487,897; 5,324,519; 5,278,201; 5,717,030; 5,744,153; 5,990,194; 5,725,491; 5,733,950; 5,763,152; 5,739,176; 5,759,563; 5,780,044; 5,792,469; 5,888,533; 5,945,115; and references cited therein. Examples of suitable biodegradable thermoplastic polyesters include polylactides, polyglycolides, polycaprolactones, a polyanhydride, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyphosphoesters, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid) polymers, polymaleic anhydrides, poly(methylvinyl) ethers, poly(amino acids), chitin, chitosan, copolymers thereof, terpolymers thereof, and combinations thereof. Preferably, the biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination (i.e., mixture) thereof. More preferably, the biodegradable thermoplastic polyester is poly (DL-lactide-co-glycolide).

The type, molecular weight, and amount of biodegradable thermoplastic polyester present in the composition will typically depend upon the desired properties of the controlled release implant. For example, the type, molecular weight, and amount of biodegradable thermoplastic polyester can influence the length of time in which the antihyperalgesic opiate is released from the controlled release implant. Specifically, in one embodiment of the present invention, the composition can be used to formulate a delivery system of an antihyperalgesic opiate that can be administered about once per three days to about once per thirty days. In such an embodiment of the present invention, the biodegradable thermoplastic polyester can preferably be poly (DL-lactide-co-glycolide); can be present in about 10 wt.% to about 80 wt.% of the composition; and can have an average molecular weight of about 4,000 to about 45,000.

The terminal groups of the poly(DL-lactide-co-glycolide) can either be hydroxyl, carboxyl, or ester depending upon the method of polymerization. Polycondensation of lactic or glycolic acid will provide a polymer with terminal hydroxyl and carboxyl groups. Ring-opening polymerization of the cyclic lactide or glycolide monomers with water, lactic acid, or glycolic acid will provide polymers with the same terminal groups. However, ring-opening of the cyclic monomers with a monofunctional alcohol such as methanol, ethanol, or 1-dodecanol will provide a polymer with one hydroxyl group and one ester terminal groups. Ring-opening polymerization of the cyclic monomers with a diol such as 1,6-hexanediol or polyethylene glycol will provide a polymer with only hydroxyl terminal groups.

Thermoplastic Polyester Molecular Weight

The molecular weight of the polymer used in the present invention can affect the rate of antihyperalgesic opiate release as long as the flowable composition has been used as an intermediate. Under these conditions, as the molecular weight of the polymer increases, the rate of antihyperalgesic opiate release from the system decreases. This phenomenon can be advantageously used in the formulation of systems for the controlled release of loperamide. For relatively quick release of antihyperalgesic opiate, low molecular weight polymers can be chosen to provide the desired release rate. For release of a antihyperalgesic opiate over a relatively long period of time, a higher polymer molecular weight can be chosen. Accordingly, a polymer system can be produced with an optimum polymer molecular weight range for the release of antihyperalgesic opiate over a selected length of time.

The molecular weight of a polymer can be varied by any of a variety of methods. The choice of method is typically determined by the type of polymer composition. For example, if a thermoplastic polyester is used that is biodegradable by hydrolysis, the molecular weight can be varied by controlled hydrolysis, such as in a steam autoclave. Typically, the degree of polymerization can be controlled, for example, by varying the number and type of reactive groups and the reaction times.

Biocompatible Organic Solvent

Any suitable biocompatible organic solvent can be employed, provided the biocompatible organic solvent is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester. Suitable biocompatible organic solvents are disclosed, e.g., in Aldrich Handbook of Fine Chemicals and Laboratory Equipment, Milwaukee, WI (2000); U.S. Patent Nos. 4,938,763; 5,707,647; 5,702,716; 5,632,727; 5,599,552; 5,487,897; 5,324,519; 5,278,201; 5,717,030; 5,744,153; 5,990,194; 5,725,491; 5,733,950; 5,763,152; 5,739,176; 5,759,563; 5,780,044; 5,792,469; 5,888,533; 5,945,115; and references cited therein.

In one embodiment of the present invention, the biocompatible organic solvent is N-methyl-2-pyrrolidone, 2-pyrrolidone, 2-ethoxyethanol, 2-ethoxyethyl acetate, ethyl acetate, ethyl lactate, ethyl butyrate, diethyl malonate, diethyl glutarate, tributyl citrate, acetyl-tri-n-hexylcitrate, diethyl succinate, tributyrin, isopropyl myristate, propylene carbonate, dimethyl carbonate, ethylene glycol dimethyl ether, propylene glycol, 1,3-butylene glycol, ϵ -caprolactone, γ -butyrolactone, N,N-dimethylformamide, dimethylacetamide, dimethyl sulfoxide, dimethyl sulfone, caprolactam, decylmethylsulfoxide, oleic acid, N,N-dimethyl-m-toluamide, 2,2 dimethyl-1,3-dioxolane-4-methanol, triacetin, ethyl acetate, benzyl alcohol, benzyl benzoate, solketal, glycofurol, 1-dodecylazacycloheptan-2-one, or any combination thereof.

In another embodiment of the present invention, the biocompatible organic solvent is a polar aprotic solvent. The polar aprotic solvents can have an amide group, an ester group, a carbonate group, a ketone, an ether, a sulfonyl group, or a combination thereof. Suitable polar aprotic solvents include, e.g., N-methyl-2-pyrrolidone, 2-pyrrolidone, N, N-dimethylformamide, dimethyl sulfoxide, propylene carbonate, caprolactam, triacetin, ethyl acetate, or any combination thereof. Preferably, the polar aprotic solvent is N-methyl-2-pyrrolidone.

The suitable biocompatible organic solvent should be able to diffuse into body fluid so that the flowable composition coagulates or solidifies.

It is also preferred that the biocompatible organic solvent for the biodegradable polymer be non-toxic and otherwise biocompatible.

5 The biocompatible organic solvent can be present in any suitable amount, provided the biocompatible organic solvent is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester. The type and amount of biocompatible organic solvent present in the composition will typically depend upon the desired properties of the controlled release implant. For example, the type and amount of biocompatible organic solvent can influence the length of time in which the antihyperalgesic opiate is released from the controlled release implant. Specifically, in one embodiment of the present invention, the composition can be used to formulate delivery system of antihyperalgesic opiate that can be administered about once per three days to about once per thirty days. In such an embodiment, the biocompatible organic solvent can preferably be N-methyl-2-pyrrolidone and can preferably be present in about 20 wt.% to about 90 wt.% of the composition.

10 The solubility of the biodegradable thermoplastic polyesters in the various biocompatible organic solvents will differ depending upon their crystallinity, their hydrophilicity, hydrogen-bonding, and molecular weight. Thus, not all of the biodegradable thermoplastic polyesters will be soluble in the same biocompatible organic solvent, but each biodegradable thermoplastic polymer or copolymer should have its appropriate biocompatible organic solvent. Lower molecular-weight polymers will normally dissolve more readily in the solvents than high-molecular-weight polymers. As a result, the concentration of a polymer dissolved in the various solvent will differ depending upon type of polymer and its molecular weight. Conversely, the higher molecular-weight polymers will normally tend to coagulate or solidify faster than the very low-molecular-weight polymers. Moreover the higher molecular-weight polymers will tend to give higher solution viscosities than the low-molecular-weight materials.

25 30 For example, low-molecular-weight polylactic acid formed by the condensation of lactic acid will dissolve in N-methyl-2-pyrrolidone(NMP) to give a 73% by weight solution which still flows easily through a 23-gauge

syringe needle, whereas a higher molecular-weight poly(DL-lactide) (DL-PLA) formed by the additional polymerization of DL-lactide gives the same solution viscosity when dissolved in NMP at only 50% by weight. The higher molecular-weight polymer solution coagulates immediately when placed into water. The low-molecular-weight polymer solution, although more concentrated, tends to coagulate more slowly when placed into water.

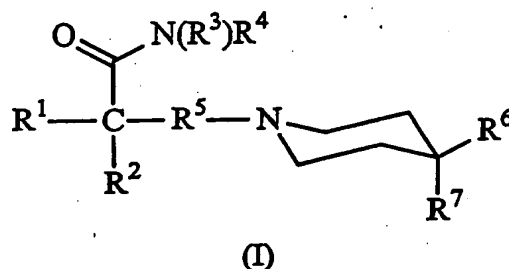
It has also been found that solutions containing very high concentrations of high-molecular-weight polymers sometimes coagulate or solidify slower than more dilute solutions. It is suspected that the high concentration of polymer impedes the diffusion of solvent from within the polymer matrix and consequently prevents the permeation of water into the matrix where it can precipitate the polymer chains. Thus, there is an optimum concentration at which the solvent can diffuse out of the polymer solution and water penetrates within to coagulate the polymer.

Antihyperalgesic Opiate

As used herein, "hyperalgesia" refers to extreme sensitiveness to pain stimuli. Stedman's Medical Dictionary, 25th ed., Williams & Wilkins, Baltimore, MD (1990). As such, an antihyperalgesic compound is a compound that effectively provides relief from an extreme sensitiveness to pain stimuli. The antihyperalgesic compound effectively reduces or eliminates the pain perception. As used herein, "opiate" refers to a narcotic drug that contains opium, derivatives of opium, or any of several semisynthetic drugs with opium like activity. Mosby's Medical Nursing, & Allied Health Dictionary, 5th ed., Mosby, St. Louis, MO (1998).

Any suitable antihyperalgesic opiate can be employed in the present invention, provided the antihyperalgesic opiate effectively reduces or eliminates pain perception in a mammal (e.g., human). The antihyperalgesic opiate can be a kappa (κ) or mu (μ) agonist. In addition, the antihyperalgesic opiate can be a non central nervous system (CNS) type opiate (e.g., methyl morphine). Suitable antihyperalgesic opiates are disclosed, e.g., in U.S. Patent Nos. 5,811,078; 5,763,445; 5,760,023; 5,744,458; 5,849,762; 3,714,159; 5,798,093; and references cited therein.

In one embodiment of the present invention, the antihyperalgesic opiate is a compound of formula (I):



5 wherein

R^1 is aryl, heteroaryl, aryl (C_1 - C_6)alkyl, or heteroaryl (C_1 - C_6)alkyl;

R^2 is aryl, heteroaryl, aryl (C_1 - C_6)alkyl, or heteroaryl (C_1 - C_6)alkyl;

10

R^3 is (C_1 - C_6)alkyl;

R^4 is (C_1 - C_6)alkyl;

R^5 is (C_1 - C_6)alkyl;

R^6 is cyano, halo, hydroxy, NR^8R^9 or $COOR^{10}$;

R^7 is aryl, heteroaryl, aryl (C_1 - C_6)alkyl, or heteroaryl (C_1 - C_6)alkyl;

15

wherein any aryl, heteroaryl, or alkyl of R^1 - R^7 is optionally substituted on carbon with one or more (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy, cyano, halo, nitro, trifluoromethyl, hydroxy, NR^8R^9 , $COOR^{10}$, SR^{11} , or $CON(H)R^{12}$;

R^8 - R^{12} are each independently hydrogen or (C_1 - C_6)alkyl;

20

or a pharmaceutically acceptable salt thereof.

A specific value for R^1 is phenyl.

A specific value for R^2 is phenyl.

A specific value for R^3 is methyl.

A specific value for R^4 is methyl.

25

A specific value for R^5 is ethyl.

A specific value for R^6 is hydroxy.

A specific value for R^7 is para-chlorophenyl.

A specific antihyperalgesic opiate is Loperamide, which is chemically designated as 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl- α,α -diphenyl-1-piperidinebutanamide; or a pharmaceutically acceptable salt thereof.

5 The amount of antihyperalgesic opiate incorporated into the flowable, in-situ, solid forming implant depends upon the desired release profile, the concentration of antihyperalgesic opiate required for a biological effect, the length of time that the antihyperalgesic opiate has to be released for treatment, and the specific antihyperalgesic opiate employed. There is no critical upper
10 limit on the amount of antihyperalgesic opiate incorporated into the polymer solution except for that of an acceptable solution or dispersion viscosity for injection through a syringe needle. The lower limit of antihyperalgesic opiate incorporated into the delivery system is dependent simply upon the activity of the antihyperalgesic opiate and the length of time needed for treatment. Specifically, in one embodiment of the present invention, the composition can be
15 used to formulate delivery system of antihyperalgesic opiate that can be administered about once per three days to about once per thirty days. In such an embodiment, the antihyperalgesic opiate can preferably be Loperamide and can preferably present in about 1.0 wt.% to about 20.0 wt.% of the composition.

Typically, the antihyperalgesic opiate can be added to a solution
20 of the polymer in the solvent. The antihyperalgesic opiate can either dissolve in the solution or be dispersed as a fine suspension. The combination of antihyperalgesic opiate and polymer solution can then be filled into a syringe. In another approach, the polymer/solvent solution can be filled into a syringe and the antihyperalgesic opiate can be filled in another syringe. The antihyperalgesic
25 opiate can optionally be dissolved in the solvent. The two syringes can then be coupled together and the contents can be drawn back and forth between the two syringes until the polymer/solvent solution and the antihyperalgesic opiate are effectively mixed together, forming a flowable composition. The flowable composition can be drawn into one syringe. The two syringes can then be
30 disconnected. A needle can be inserted onto the syringe containing the flowable composition. The flowable composition can then be injected through the needle into the body. The flowable composition can be formulated and administered to a patient as described in, e.g., U.S. Patent Nos. 5,324,519; 4,938,763; 5,702,716;

5,744,153; and 5,990,194; or as described herein. Once in place, the solvent dissipates, the remaining polymer solidifies, and a solid structure is formed. The solvent will dissipate and the polymer will solidify and entrap or encase the antihyperalgesic opiate within the solid matrix.

5 The release of antihyperalgesic opiate from these solid implants will follow the same general rules for release of a drug from a monolithic polymeric device. The release of antihyperalgesic opiate can be affected by the size and shape of the implant, the loading of antihyperalgesic opiate within the implant, the permeability factors involving the antihyperalgesic opiate and the
10 particular polymer, and the degradation of the polymer. Depending upon the amount of antihyperalgesic opiate selected for delivery, the above parameters can be adjusted by one skilled in the art of drug delivery to give the desired rate and duration of release.

15 Glucocorticoid

 In one embodiment of the present invention, the flowable composition, biodegradable implant formed in situ, solid implant, or combination thereof, can optionally include a glucocorticoid (e.g.,
20 betamethasone) to diminish the likelihood that there will be erythema, edema, or a combination thereof to surrounding tissue. The glucocorticoid can be present in any suitable and appropriate amount, provided the amount of glucocorticoid effectively diminishes the likelihood that there will be erythema, edema, or a combination thereof to surrounding tissue. Typically, up to about 1 wt% glucocorticoid (e.g., betamethasone), up to about 0.1 wt.% glucocorticoid (e.g.,
25 betamethasone), or up to about 0.05 wt.% glucocorticoid (e.g., betamethasone) can be present in the flowable composition, biodegradable implant formed in situ, solid implant, or combination thereof.

30 Dosages

 The amount of flowable composition administered will typically depend upon the desired properties of the controlled release implant. For example, the amount of flowable composition can influence the length of time in which the antihyperalgesic opiate is released from the controlled release implant.

Specifically, in one embodiment of the present invention, the composition can be used to formulate delivery system of antihyperalgesic opiate that can be administered about once per three days to about once per thirty days. In such an embodiment, about 0.10 mL to about 5.0 mL of the flowable composition can be administered.

Controlled Release Delivery

The flowable composition of the present invention can incorporate the biocompatible organic solvent, thermoplastic polyester, and active agent (i.e., antihyperalgesic opiate) into a controlled release delivery system with a low initial drug burst, as described in U.S. Patent Nos. 4,938,763; 5,278,201; 5,278,202; 5,780,044; U.S. Ser. No. 09/643,289; and references cited therein. For example, the controlled release delivery system can include a controlled release component that includes a microstructure (e.g. a microcapsule) or macrostructure (e.g. a film or fiber) controlled release system, a molecular controlled release system (e.g. a polymer/drug conjugate) or a combination thereof, as described in U.S. Patent No. 5,780,044; and references cited therein. Alternatively, the controlled release delivery system can include a controlled release additive [e.g., poly(lactide-co-glycolide)/polyethylene glycol (PLG/PEG) block copolymer], as described in U.S. Ser. No. 09/643,289; and references cited therein. The controlled release delivery system employed herein offers the advantage of allowing the in situ formation of an implant while reducing or eliminating the initial burst effect usually encountered with many liquid drug delivery systems.

All publications, patents, and patent documents are incorporated by reference herein, as though individually incorporated by reference. The invention will now be illustrated with the following non-limiting examples.

Examples

30

The examples can be performed as illustrated herein below:

Example 1

Poly(DL-lactide-co glycolide) with 50:50 molar ratio of lactide to glycolide, a molecular weight of 12,000 daltons, and a carboxyl endgroup (RG 502H, Boehringer Ingelheim) is dissolved in N-methyl-2-pyrrolidone (NMP) at a concentration of 40% by weight. To this solution is added loperamide hydrochloride to provide a mixture with 10% by weight drug. The mixture consisting of a uniform suspension of the drug in the controlled release formulation is sterilized by gamma irradiation at 25 Kilograys. The resulting product can be injected into tissue using a 1-cc polypropylene syringe with a 20 gauge needle to provide a sustained release of the drug at the site of injection.

Example 2

Poly(DL-lactide-co glycolide) with 50:50 molar ratio of lactide to glycolide, a molecular weight of 6,000 daltons, and a carboxyl endgroup (RG 501H, Boehringer Ingelheim) is dissolved in N-methyl-2-pyrrolidone (NMP) at a concentration of 45% by weight. Loperamide hydrochloride is added to this solution at a 10% by weight to provide a uniform suspension. After sterilization by gamma irradiation at 25 Kilograys, the formulation can be injected into tissue using a 1-cc polypropylene syringe with a 20-gauge needle to provide a sustained release of the drug at the site of injection.

Example 3

The same polymer described in Example 1 is dissolved in NMP at 35% by weight. To this solution is added 5% by weight poly(DL-lactide-co-glycolide-co-polyethylene glycol) (PLG-PEG) with a 50:50 molar ratio of lactide to glycolide and 5% by weight polyethylene glycol. The polyethylene glycol block of the copolymer has a molecular weight of 5,000 daltons and the entire PLG-PEG block copolymer has a molecular weight of about 100,000 daltons. Loperamide hydrochloride is added to this solution at a 10% by weight to provide a uniform suspension of drug in the controlled release formulation. After sterilization by gamma irradiation at 25 Kilograys, the formulation can be injected into tissue using a 1-cc polypropylene syringe with a 20-gauge needle to provide a sustained release of the drug at the site of injection.

Example 4

The same copolymer described in Example 2 is dissolved in NMP at 40% by weight, and the PLG-PEG block copolymer described in Example 3 is added at 5% by weight. Loperamide hydrochloride is added to this solution at a 10% by weight to provide a uniform suspension of drug in the controlled release formulation. After sterilization by gamma irradiation at 25 Kilograys, the formulation can be injected into tissue using a 1-cc polypropylene syringe with a 20-gauge needle to provide a sustained release of the drug at the site of injection.

Example 5

The polymer solution described in Example 1 is filled into an irradiation-resistant polypropylene syringe with a male luer lock fitting, and sterilized by gamma irradiation at 25 Kilorays. Loperamide hydrochloride as a dry powder is loaded into another polypropylene syringe with a female luer lock fitting, and sterilized by gamma irradiation. The two syringes are then coupled together, the contents mixed back and forth between the two syringes immediately before use. After mixing to provide a uniform suspension, the contents are transferred to the syringe with a male luer lock fitting, the syringes decoupled, and a 20-gauge needle attached to the male luer lock fitting for injection into tissue where the polymer formulation solidified to form a solid depot for sustained deliver of the drug at the site of injection.

Example 6

The following two formulations were prepared by dissolving loperamide HCl and dexamethasone into γ -irradiated polymer solution.

1. 30% 50/50 PLGH (InV 0.1)/70% NMP with 2% loperamide HCl
2. 30% 50/50 PLGH (InV 0.1)/70% NMP with 2% loperamide HCl and 0.05% dexamethasone

Two groups of rats (10 per treatment group) were administered ~0.1 ml of one of the above formulations by IM injection. On day 1 and day 3 implants were removed for subsequent HPLC analysis of loperamide. Macroscopic tissue reaction to each formulation was also evaluated. Formulation 1 and 2 had 53% and 62% initial burst on day 1, respectively. On day 3 they had 74% and 75%

release of loperamide HCl. Formulation 1 caused minimal to mild erythema and edema up to day 1. These tissue reactions were gone by day 3. Formulation 2 caused minimal to mild erythema up to day 1 and that was gone by day 3.

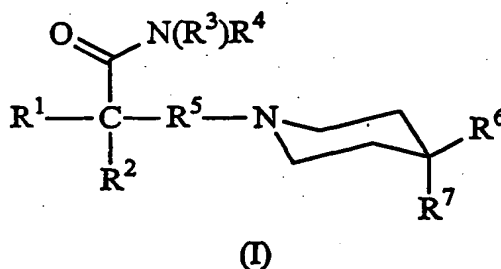
However, no edema was observed with the formulation containing dexamethasone.

5

CLAIMS

What is claimed is:

- 5 1. A flowable composition suitable for use as a controlled release implant, the composition comprising:
- (a) a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid;
- 10 (b) a biocompatible organic solvent that is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester; and
- (c) an antihyperalgesic opiate.
- 15 2. The composition of claim 1 wherein the biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a polycaprolactone, a polyanhydride, a polyamide, a polyurethane, a polyesteramide, a polyorthoester, a polydioxanone, a polyacetal, a polyketal, a polycarbonate, a polyorthocarbonate, a polyphosphazene, a polyphosphoester, a polyhydroxybutyrate, a polyhydroxyvalerate, a polyalkylene oxalate, a polyalkylene succinate, a poly(malic acid) polymer, a polymaleic anhydride, a poly(methylvinyl) ether, a poly(amino acid), chitin, chitosan, a copolymer thereof, a terpolymer thereof, or any combination thereof.
- 20 3. The composition of claim 1 wherein the biodegradable thermoplastic polyester is a polylactide, a polyglycolide, a copolymer thereof, a terpolymer thereof, or a combination thereof.
- 25 4. The composition of claim 1 wherein the biodegradable thermoplastic polyester is poly (DL-lactide-co-glycolide).
- 30 5. The composition of claim 1 wherein the biodegradable thermoplastic polyester is present in about 10 wt.% to about 80 wt.% of the composition.



wherein

R^1 is aryl, heteroaryl, aryl (C_1 - C_6)alkyl, or heteroaryl (C_1 - C_6)alkyl;

5 R^2 is aryl, heteroaryl, aryl (C_1 - C_6)alkyl, or heteroaryl (C_1 - C_6)alkyl;

R^3 is (C_1 - C_6)alkyl;

R^4 is (C_1 - C_6)alkyl;

R^5 is (C_1 - C_6)alkyl;

10 R^6 is cyano, halo, hydroxy, NR^8R^9 or $COOR^{10}$;

R^7 is aryl, heteroaryl, aryl (C_1 - C_6)alkyl, or heteroaryl (C_1 - C_6)alkyl;

wherein any aryl, heteroaryl, or alkyl of R^1 - R^7 is optionally substituted on carbon with one or more (C_1 - C_6)alkyl, (C_1 - C_6)alkoxy, cyano, halo, nitro, trifluoromethyl, hydroxy, NR^8R^9 , $COOR^{10}$, SR^{11} , or $CON(H)R^{12}$;

15 R^8 - R^{12} are each independently hydrogen or (C_1 - C_6)alkyl; or a pharmaceutically acceptable salt thereof.

13. The composition of claim 12 wherein R^1 is phenyl, R^2 is phenyl, R^3 is methyl, R^4 is methyl, R^5 is ethyl, R^6 is hydroxy, and R^7 is para-chlorophenyl.

14. The composition of claim 1 wherein the antihyperalgesic opiate is a non central nervous system type opiate.

15. The composition of claim 1 wherein the antihyperalgesic opiate is 4-(4-chlorophenyl)-4-hydroxy-N,N-dimethyl- α,α -diphenyl-1-piperidinebutanamide; or a pharmaceutically acceptable salt thereof.

5 16. The composition of claim 1 wherein the antihyperalgesic opiate is present in about 1.0 wt.% to about 20.0 wt.% of the composition.

17. The composition of claim 16 having a volume of about 0.1 mL to about 5.0 mL.

10 18. The composition of claim 16 that is formulated for administration about once per three days to about once per thirty days.

19. The composition of claim 1 further comprising a glucocorticoid.

15 20. The composition of claim 19 wherein the glucocorticoid is betamethasone.

20 21. A method for forming a flowable composition for use as a controlled release implant, comprising the step of mixing, in any order:

(a) a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid;

25 (b) a biocompatible organic solvent that is miscible to dispersible in aqueous medium or body fluid and effectively dissolves the thermoplastic polyester; and

(c) an antihyperalgesic opiate.

wherein the mixing is performed for a sufficient period of time effective to form the flowable composition for use as a controlled release implant.

30 22. The method of claim 21 wherein the biocompatible thermoplastic polyester and the biocompatible organic solvent are mixed together to form a

mixture and the mixture is then mixed with the antihyperalgesic opiate to form the flowable composition.

5 23. The method of claim 21 wherein the flowable composition further comprises a glucocorticoid.

24. The method of claim 23 wherein the glucocorticoid is betamethasone.

10

25. A biodegradable implant formed in situ, in a patient, by the steps comprising:

(a) injecting a composition within the body of the patient; and

(b) allowing the biocompatible organic solvent to dissipate to

15

produce a solid biodegradable implant, wherein the composition comprises an effective amount of a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid; an effective amount of a biocompatible organic solvent that is miscible to dispersible in aqueous medium or body fluid and effectively dissolves the thermoplastic polyester; and

20

an effective amount of an antihyperalgesic opiate.

26. The biodegradable implant of claim 25 wherein the patient is a human.

25

27. The biodegradable implant of claim 25 wherein the solid implant releases the effective amount of antihyperalgesic opiate at a controlled rate as the solid implant biodegrades in the patient.

30

28. The biodegradable implant of claim 25 wherein the solid biodegradable implant adheres to tissue within the body of the patient.

29. The biodegradable implant of claim 25 wherein the composition further comprises a glucocorticoid.

30. The biodegradable implant of claim 29 wherein the glucocorticoid is betamethasone.

31. A method of forming a biodegradable implant in situ, in a living patient, comprising the steps of:

(a) injecting a flowable composition within the body of a patient; and

(b) allowing the biocompatible organic solvent to dissipate to produce a solid biodegradable implant, wherein the flowable composition comprises an effective amount of a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid; an effective amount of a biocompatible organic solvent that is miscible to dispersible in aqueous medium or body fluid and effectively dissolves the thermoplastic polyester; and an effective amount of an antihyperalgesic opiate.

32. The method of claim 31 wherein the solid biodegradable implant releases the effective amount of antihyperalgesic opiate by diffusion, erosion, or a combination of diffusion and erosion as the solid implant biodegrades in the patient.

33. The method of claim 31 wherein the flowable composition further comprises a glucocorticoid.

34. The method of claim 33 wherein the glucocorticoid is betamethasone.

35. A method of treating or preventing pain in a patient comprising administering to the patient in need of such treatment or prevention an effective amount of a flowable composition of any one of claims 1-20.

36. The method of claim 35 wherein the patient is a human.

37. The method of claim 35 wherein the flowable composition causes little or no erythema, edema, or combination thereof, to surrounding tissue.

38. A kit comprising:

5 (a) a first container comprising a composition comprising a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid and a biocompatible organic solvent that is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester; and

10 (b) a second container comprising an antihyperalgesic opiate.

39. The kit of claim 38 wherein the first container is a syringe.

40. The kit of claim 38 wherein the second container is a syringe.

15 41. The kit of claim 38 further comprising instructions.

42. The kit of claim 38 wherein the first container can be connected to the second container.

20 43. The kit of claim 38 wherein the first container and the second container are each configured to be directly connected to each other.

25 44. The kit of claim 38 wherein the composition further comprises a glucocorticoid.

45. The kit of claim 38 wherein the glucocorticoid is betamethasone.

46. A solid implant comprising:

30 (a) a biocompatible thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid; and

(b) an antihyperalgesic opiate; wherein

the solid implant has a solid or gelatinous microporous matrix,
the matrix being a core surrounded by a skin.

5 47. The solid implant of claim 46 further comprising a biocompatible
organic solvent that is miscible to dispersible in aqueous or body fluid and can
effectively dissolve the thermoplastic polyester.

10 48. The solid implant of claim 47 wherein the amount of
biocompatible organic solvent is minimal.

 49. The solid implant of claim 47 wherein the amount of
biocompatible organic solvent decreases over time.

15 50. The solid implant of claim 46 wherein the core contains pores of
diameters from about 1 to about 1000 microns.

 51. The solid implant of claim 46 wherein the skin contains pores of
smaller diameters than those of the core pores.

20 52. The solid implant of claim 46 wherein the skin pores are of a size
such that the skin is functionally non-porous in comparison with the core.

 53. The solid implant of claim 46 wherein the composition further
comprises a glucocorticoid.

25 54. The solid implant of claim 53 wherein the glucocorticoid is
betamethasone.

30 55. A delivery system comprising:
(a) a biodegradable thermoplastic polyester that is at least
substantially insoluble in aqueous medium or body fluid;

(b) a biocompatible organic solvent that is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester; and

(c) an antihyperalgesic opiate;

wherein the delivery system controllably releases the antihyperalgesic opiate over a period of time.

56. The delivery system of claim 55 further comprising a controlled release component that includes a microstructure controlled release system, a macrostructure controlled release system, a molecular controlled release system, or a combination thereof.

57. The delivery system of claim 56 wherein the microstructure controlled release system comprises a microcapsule.

58. The delivery system of claim 56 wherein the macrostructure controlled release system comprises a film, a fiber, a rod, a disk, a cylinder, or a combination thereof.

59. The delivery system of claim 56 wherein the molecular controlled release system comprises a polymer or drug conjugate.

60. The delivery system of claim 55 further comprising a controlled release additive.

61. The delivery system of claim 60 wherein the controlled release additive is a poly(lactide-co-glycolide)/polyethylene glycol (PLG/PEG) block copolymer.

62. The delivery system of claim 55 having no appreciable initial burst of the antihyperalgesic opiate.

63. The delivery system of claim 55 wherein the period of time is about three days to about thirty days.

64. The delivery system of claim 55 wherein the composition further comprises a glucocorticoid.

65. The delivery system of claim 64 wherein the glucocorticoid is betamethasone.

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(54) Title: **INJECTABLE SUSTAINED RELEASE DELIVERY SYSTEM WITH LOPERAMIDE**

(57) Abstract: The present invention provides for a flowable composition suitable for use as a controlled release implant, a method for forming a flowable composition for use as a controlled release implant, and methods for using the flowable composition. The composition comprises a biodegradable thermoplastic polyester that is at least substantially insoluble in aqueous medium or body fluid; a biocompatible organic solvent that is miscible to dispersible in aqueous medium or body fluid and can effectively dissolve the thermoplastic polyester; and an antihyperalgesic opiate.

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Minimum documentation searched (classification system followed by classification symbols)

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WPI Data, PAJ, EPO-Internal, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| A | WO 00 24374 A (ATRIX LABORATORIES, INC.) 4 May 2000 (2000-05-04) the whole document | 1-65 |
| A | WO 91 18940 A (NOVA PHARMACEUTICAL CORPORATION) 12 December 1991 (1991-12-12) page 4 -page 6 page 25 -page 26; example 7 claim 13 | 1-65 |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search

28 August 2002

Date of mailing of the international search report

05/09/2002

Name and mailing address of the ISA

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Authorized officer

Benz, K

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/47116

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|--|
| P, X | <p>WO 01 35929 A (ATRIX LABORATORIES, INC.) 25 May 2001 (2001-05-25)</p> <p>claims 1-20 page 40, line 9</p> | <p>1-11, 14, 21, 22, 25-28, 31, 32, 35, 46-52, 55-58</p> |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/47116**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 25-37 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/47116

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
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